REMARKS

The Applicant respectfully requests reconsideration of the pending, elected claims 8-17.

Amendments to the Specification and Drawings

The Applicant offers amendments to the specification, as set forth earlier, to correct typographical errors existing in the original application. The Applicant also offers an amendment to the sheet containing drawing Fig. 3B, which is attached, in order to correct two spelling errors appearing on the original figure. As amended, the Applicant submits the specification and drawings are placed in proper form for allowance.

Objection to Claim 18

Claim 18 was objected to under 37 CFR §1.75(c) as being a dependent claim of improper form for failing to further limit the subject matter of a previous claim. Claim 18, however, appears to be drafted as an independent claim. As well, claim 18 is currently in a withdrawn status, having not been elected. The Applicant respectfully requests clarification regarding the objection.

Indefiniteness

Claim 1 was rejected under 35 U.S.C. §112 second paragraph for being indefinite with regard to the use of the terms "embryonic stem cells" and "human embryonic stem cell." Considering the discussion on page 2 of the office action, the Applicant believes the rejection is directed toward claim 8, rather than claim 1. Accordingly, the Applicant amends claim 8 by inserting the word "human" before the words "embryonic stem cell" in step a and replaces the word "human" with the word "said" in step c to clarify which embryonic cells are being referred to in step c. Thus, the Applicant submits that amended claim 8 complies with the requirements of 35 U.S.C. §112, second paragraph.

Obviousness

Pending claims 8-17 stand rejected under 35 U.S.C. §103(a) as being obvious over various combinations of Thomson et al. (Science, Vol. 282, pp.1145-1147 (1998)); Keller (Curr. Opin. in Cell Biology, Vol. 7, pp. 862-869 (1995)); Wobus et al. (Cell Diff., Vol. 20, p. 81S (1987)); Vittet et al. (Blood, Vol. 88, pp. 3424-3431 (1996)); and Drab et al. (FASEB Journal, Vol. 11, pp. 905-915 (1997)). Assuming without conceding that the cited art collectively sets forth the elements of claims 8-17, the pending claims are still patentable because (i) the teachings of the cited art do not indicate a reasonable expectation of success and (ii) no suggestion or motivation exists to combine the references to teach the novel methods of the claims.

Claims 8-16 define methods for directing differentiation of human embryonic cells to a specific cell type by forming embryoid bodies from human ESCs and causing differentiation of human embryonic cells with an exogenous factor. Claim 17 defines a method for mapping a pathway of differentiation of a population of human embryonic cells by using an exogenous factor. Thus all pending claims are directed specifically toward *human* embryonic cells.

Keller, Wobus, Vittet, and Drab are all directed toward aspects of in vitro differentiation of embryonic stem cells ("ESCs"). The techniques discussed in the references for forming differentiated ESCs are focused almost entirely on *murine* ESCs. None of the references discusses the use of the revealed techniques as applied to *human* ESCs or *human* embryonic cells, as required by the pending claims.

Thomson teaches the production of human ESCs. Thomson, however, does not reveal any of the steps of claims 8-16 to direct differentiation of human embryonic cells, or any of the steps of claim 17 to map a pathway to differentiate human embryonic cells.

Even assuming without conceding that Keller, Wobus, Vittet, and Drab collectively set forth the steps of claims 8-17 as directed toward differentiation of

mouse embryonic cells, a prima facie case of obviousness cannot be maintained against the pending claims.

1. *No Reasonable Expectation of Success*

No reasonable expectation of success exists to apply the techniques in Keller, Wobus, Vittet, and Drab to human embryonic cells because of the differences between mouse embryonic cells and human embryonic cells. Mouse ESCs, being derived from mouse blastocysts that are flushed from pregnant mice, have different cell surface markers than are present on human ESCs. As a result, the mouse ESCs follow different cues for their differentiation than human ESCs. As well, the timing of early embryogenesis is much faster in mice than humans. Thus, growth factors that influence early embryonic development cannot be expected to influence mouse and human development in a similar manner. Thus, one skilled in the art cannot expect the same results from both human and mouse ESCs upon treatment with different differentiation protocols.

As reviewed by Elsea (ILAR J., Vol. 43, No. 2, pp. 66-79 (2002)), mice that are created using gene knockout technology in ESCs to mimic human disease phenotypes exhibit major genetic differences in comparison to humans, potentially making the two species incomparable (a copy of the reference is attached). For example, the mouse model for Lesch-Nyhan disease does not mimic the human condition (see Elsea at 67-69). As well, many mouse models of metabolic diseases have not mimicked the human condition, stressing the genetic differences between the two species (see Elsea, Table 1 at 67). Thomson states that human ESCs are particularly valuable for the study of the development and function of tissues that differ between mice and humans, noting that the placenta, extraembryonic membranes, and egg cylinder of mice all differ substantially from the corresponding structure in the human embryo (see Thomson, cols. 1 and 2 at 1146). Thus, no reasonable expectation of success in applying the differentiation techniques used for mouse ESCs in Keller, Wobus,

Vittet, and Drab to human ESCs exists in light of the differences between the species.

In particular, Thomson and Marshall (Curr. Top. Dev. Biol., Vol. 38, pp. 133-165 (1998)) note that ESCs derived from rhesus monkeys, do not behave the same as mouse ESCs (a copy of the reference is attached). For example, rhesus monkey ESCs do not have the capacity to fully create mature cystic embryoid bodies like mouse ESCs. These findings support the notion that there is no reasonable expectation to apply techniques for mouse ESCs to human ESCs since rhesus monkeys are primates and closer biologically to humans than mice. Thomson states that rhesus monkey ESCs provide an accurate model to develop strategies to demonstrate the safety and efficacy of ESC-based therapies (see Thomson, col. 1, at 1147). As well, the differences in formation of embryoid bodies from ESCs in rhesus monkeys and mice, the formation of such bodies being a necessary step of claims 8-16, point away from applying the techniques in Keller, Wobus, Vittet, and Drab to human ESCs as required by the claims.

Since one skilled in the art could not maintain a reasonable expectation of success in applying the techniques of Keller, Wobus, Vittet, and Drab to human ESCs as required by claims 8-17, a prima facie case of obviousness cannot be maintained against the pending claims.

2. *No Motivation to Combine References*

No suggestion or motivation exists to combine the teachings of any one of Keller, Wobus, Vittet, and Drab with Thomson to teach any of the methods defined by pending claims 8-17. No implicit suggestion of motivation to combine the references exists because, as discussed earlier, no reasonable expectation of success exists to those skilled in the art to use the techniques for mouse ESCs in Keller, Wobus, Vittet, and Drab for human ESCs as discussed by Thomson. In addition, no explicit suggestion or motivation in any of the references to apply the techniques of Keller, Wobus, Vittet, and Drab to human ESCs exists.

The office action indicates that Thomson offers motivation by stating that "while substantial advances need to be made in the directed differentiation of human ES cells, progress in the directed differentiation of mouse ES cells . . . has been made" (see office action at 3). The relevant statements read in the context of Thomson's article, however, do not suggest or motivate one to use techniques utilized for mouse ESCs on human ESCs. Thomson states that "substantial advances in basic developmental biology are required" to direct human ESCs (see Thomson at 1147). The sentences following this statement simply underscore Thomson's conclusion that human ESCs will eventually link the progress of basic developmental biology with the prevention and treatment of human disease; there is no explicit or implicit suggestion or motivation that the techniques used for mouse ESCs can be applied to human ESCs.

The office action also states that Keller motivates the combining of references since it teaches that "embryoid bodies provide an approach for defining the earliest steps of commitment from respective precursor population" (see office action at 3-4). The statement, however, does not provide any suggestion or motivation that techniques used in forming embryoid bodies from mouse ESCs are applicable to forming embryoid bodies from human ESCs.

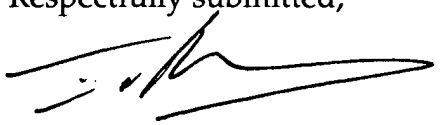
Without suggestion or motivation to combine the references, a prima facie case of obviousness cannot be maintained against the pending claims.

Thus, claims 8-17 are patentable over an obviousness rejection because the prima facie elements of a reasonable expectation of success and a suggestion or motivation to combine the references are not present.

Conclusion

In view of the amendments and arguments presented, the Applicant respectfully requests allowance of pending claims 8-17.

Respectfully submitted,



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